

(2) a DNA sequence encoding hPTH, wherein the leader sequence and the hPTH sequence are operably linked;

D⁷
Cont (b) culturing said microorganism to allow expression of said DNA sequence encoding hPTH, thereby producing hPTH (1-84); and

(c) purifying the resultant hPTH (1-84) protein.

D⁸ 26. The composition of claim 24, wherein the hPTH protein of step (c) has a purity of greater than 90%.

D⁹ 29. The composition of claim 27, wherein said hPTH (1-84) protein of step (c) has a purity of greater than 90%.

34. (Amended) A composition comprising recombinant parathyroid hormone (hPTH) (1-84), wherein the hPTH is made by a process comprising the steps of:

(a) providing a microorganism comprising a DNA sequence which encodes:

(1) an optimized consensus signal sequence having the following:

(i) a positively charged amino-terminal;

(ii) a hydrophobic core-region; and

(iii) a polar COOH-terminal region;

(2) a leader sequence, and

D¹⁰ (3) a DNA sequence encoding hPTH, wherein the signal sequence, the leader sequence and the sequence encoding hPTH are operably linked;

(b) culturing said microorganism to allow expression of said DNA sequence encoding hPTH, thereby producing hPTH (1-84); and

(c) purifying the resultant hPTH (1-84) protein.

36. (Amended) A composition comprising recombinant parathyroid hormone (hPTH) (1-84), wherein the hPTH is made by a process comprising the steps of:

(a) providing a microorganism comprising a DNA sequence which encodes:

(1) a leader sequence; and

(2) a DNA sequence encoding hPTH comprising a functional signal sequence encoded by an amino-terminal amino acid sequence, wherein said amino-terminal amino acid sequence is capable of directing secretion in yeast, and wherein the leader sequence and the sequence encoding hPTH are operably linked;

(b) culturing said microorganism to allow expression of said DNA sequence encoding hPTH, thereby producing hPTH (1-84); and

(c) purifying the resultant hPTH (1-84) protein.

Please add the following new claims:

Sub E1
--38. An extract obtained following growth of a microorganism transformed to express a DNA sequence encoding a fusion product in which hPTH(1-84) is fused at its N-terminus with a leader sequence, wherein:

(a) said leader sequence is cleavable by said microorganism upon production of said fusion product;

(b) said extract comprises a PTH component; and

(c) said PTH component consists essentially of intact PTH molecules.

39. An extract according to claim 38, wherein the PTH component consists of PTH molecules that are intact PTH(1-84) molecules.

40. An extract according to claim 38, wherein the extract is obtained from an organism selected from *E. coli* and yeast.

D12 Sub E2
41. A method for obtaining intact hPTH(1-84), comprising

(a) obtaining an extract following growth of a microorganism transformed to express a DNA sequence encoding a fusion product in which hPTH(1-84) is fused at its N-terminus with a leader sequence, wherein:

(i) said leader sequence is cleavable by said microorganism upon production of said fusion product;

(ii) said extract comprises a PTH component; and

(iii) said PTH component consists essentially of intact PTH molecules; and

(b) treating said extract to isolate the PTH component thereof.

42. A composition comprising recombinant human parathyroid hormone (hPTH) (1-84), wherein the hPTH is made by a process comprising the steps of:

- (a) providing a microorganism comprising a DNA sequence encoding:
- (1) a leader sequence corresponding to the DNA sequence encoding *Saccharomyces* mating factor $\alpha 1$ lacking the yeast STE13 recognition; and
 - (2) a DNA sequence encoding hPTH, wherein the leader sequence and the hPTH sequence are operably linked;
- (b) culturing said microorganism to allow expression of said DNA sequence;
- (c) isolating, following said culturing, an extract comprising a PTH component, the PTH component consisting essentially of intact hPTH(1-84); and
- (d) treating said extract to purify the hPTH (1-84) protein.

43. The composition of claim 42, wherein the microorganism is selected from the group consisting of *Escherichia coli* and yeast.

44. The composition of claim 42, wherein the hPTH(1-84) in step (c) has a purity of greater than 90%.

45. A composition comprising recombinant human parathyroid hormone (hPTH) (1-84), wherein the hPTH is made by a process comprising the steps of:

- (a) providing a microorganism comprising a DNA sequence which encodes:
- (1) the first nineteen amino acids of the DNA sequence encoding *Saccharomyces* mating factor $\alpha 1$ as a leader sequence; and
 - (2) a DNA sequence encoding hPTH, wherein the leader sequence and the sequence encoding hPTH are operably linked;
- (b) culturing said microorganism to allow expression of said DNA sequence;

(c) isolating, following said culturing, an extract comprising a PTH component, the PTH component consisting essentially of intact hPTH(1-84); and

(d) treating said extract to purify the hPTH(1-84).

46. The composition of claim 45, wherein the microorganism is selected from the group consisting of *Escherichia coli* and yeast.

47. The composition of claim 45, wherein the hPTH(1-84) in step (c) has a purity of greater than 90%.

48. A composition comprising recombinant human parathyroid hormone (hPTH) (1-84), wherein the hPTH is made by a process comprising the steps of:

(a) providing a microorganism comprising a DNA sequence which encodes:

(1) a leader sequence; and

(2) a DNA sequence encoding a derivative of hPTH, wherein the cleavage site after the pair of basic amino acids at positions 25 and 26 of the derivative hPTH gene has been modified such that the hormone is excluded as a substrate for yscF protease, wherein the leader sequence and the hPTH sequence are operably linked;

(b) culturing said microorganism to allow expression of said DNA sequence ;

(c) isolating, following said culturing, an extract comprising a PTH component, the PTH component consisting essentially of intact hPTH(1-84); and

(d) treating said extract to purify the hPTH(1-84).

49. The composition of claim 48, wherein amino acid 26 of the human hPTH gene is modified from lysine to glutamine.

50. The composition of claim 48, wherein the leader sequence is the DNA sequence encoding *Saccharomyces* mating factor $\alpha 1$.

51. The composition of claim 48, wherein the hPTH(1-84) in step (c) has a purity of greater than 90%.

52. A composition comprising recombinant parathyroid hormone (hPTH) (1-84), wherein the hPTH is made by a process comprising the steps of:

(a) providing a microorganism comprising a DNA sequence which encodes:

(1) an optimized consensus signal sequence having the following:

(i) a positively charged amino-terminal;

(ii) a hydrophobic core region; and

(iii) a polar COOH-terminal region,

(2) a leader sequence; and

(3) a DNA sequence encoding hPTH, wherein the signal sequence, the leader sequence and the sequence encoding hPTH are operably linked;

(b) culturing said microorganism to allow expression of said DNA sequence;

(c) isolating, following said culturing, an extract comprising a PTH component, the PTH component consisting essentially of intact hPTH(1-84); and

(d) treating said extract to purify the hPTH(1-84).

53. The composition of claim 52, wherein the signal sequence is encoded by an amino acid sequence selected from the group consisting of: (1) Met-Lys-Ala-Lys-Leu-Leu-Val-Leu-Leu-Thr-Ala-Phe-Val-Ala-Thr-Asp-Ala; (2) Met-Arg-Ser-Leu-Leu-Ile-Leu-Val-

Leu-Cys-Phe-Leu-Pro-Leu-Ala-Ala-Leu-Gly; and (3) Met-Arg-Phe-Pro-Ser-Ile-Phe-Thr-Ala-Val-Leu-Phe-Ala-Ala-Ser-Ser-Ala-Leu-Ala.

54. A composition comprising recombinant parathyroid hormone (hPTH) (1-84), wherein the hPTH is made by a process comprising the steps of:

(a) providing a microorganism comprising a DNA sequence which encodes:

(1) a leader sequence; and

(2) a DNA sequence encoding hPTH comprising a functional signal sequence encoded by an amino-terminal amino acid sequence, wherein said amino-terminal amino acid sequence is capable of directing secretion in yeast, and wherein the leader sequence and the hPTH sequence are operably linked;

(b) culturing said microorganism to allow expression of said DNA sequence;

(c) isolating, following said culturing, an extract comprising a PTH component, the PTH component consisting essentially of intact hPTH(1-84); and

(d) treating said extract to purify the hPTH(1-84).

55. The composition of claim 54, wherein the signal sequence is encoded by the following amino acid sequence:

Met-Asn-Ile-Phe-Tyr-Ile-Phe-Leu-Phe-Leu-Ser-Phe-Val-Gln-Gly-Thr-Arg-Gly.

56. An extract according to claim 39, wherein the extract is obtained from an organism selected from *E. coli* and yeast.--